

RECEIVED ATENT COOPERATION TTY

PCT/CA97/00745

MAY 3 1999

M. 3 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 | 6 P.M.PCT

NOTICE INFORMING THE APPLICANT OF THE COMMUNICATION OF THE INTERNATIONAL APPLICATION TO THE DESIGNATED OFFICES

(PCT Rule 47.1(c), first sentence)

Date of mailing (day/month/year) 22 April 1999 (22.04.99)
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Applicant's or agent's file reference 2139-11 PCT	IMPORTANT NOTICE
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International application No. PCT/CA97/00745	International filing date (day/month/year) 15 October 1997 (15.10.97)	Priority date (day/month/year)
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Applicant NATIONAL RESEARCH COUNCIL OF CANADA et al
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- Notice is hereby given that the International Bureau has communicated, as provided in Article 20, the international application to the following designated Offices on the date indicated above as the date of mailing of this Notice:

AU, BR, CN, EP, IL, JP, KP, KR, US

In accordance with Rule 47.1(c), third sentence, those Offices will accept the present Notice as conclusive evidence that the communication of the international application has duly taken place on the date of mailing indicated above and no copy of the international application is required to be furnished by the applicant to the designated Office(s).

- The following designated Offices have waived the requirement for such a communication at this time:

AL, AM, AP, AT, AZ, BA, BB, BG, BY, CA, CH, CU, CZ, DE, DK, EA, EE, ES, FI, GB, GE, GH, HU, ID, IS, KE, KG, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, OA, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, UZ, VN, YU, ZW

The communication will be made to those Offices only upon their request. Furthermore, those Offices do not require the applicant to furnish a copy of the international application (Rule 49.1(a-bis)).

- Enclosed with this Notice is a copy of the international application as published by the International Bureau on 22 April 1999 (22.04.99) under No. WO 99/19356

REMINDER REGARDING CHAPTER II (Article 31(2)(a) and Rule 54.2)

If the applicant wishes to postpone entry into the national phase until 30 months (or later in some Offices) from the priority date, a **demand for international preliminary examination** must be filed with the competent International Preliminary Examining Authority before the expiration of 19 months from the priority date.

It is the applicant's sole responsibility to monitor the 19-month time limit.

Note that only an applicant who is a national or resident of a PCT Contracting State which is bound by Chapter II has the right to file a demand for international preliminary examination.

REMINDER REGARDING ENTRY INTO THE NATIONAL PHASE (Article 22 or 39(1))

If the applicant wishes to proceed with the international application in the **national phase**, he must, within 20 months or 30 months, or later in some Offices, perform the acts referred to therein before each designated or elected Office.

For further important information on the time limits and acts to be performed for entering the national phase, see the Annex to Form PCT/IB/301 (Notification of Receipt of Record Copy) and Volume II of the PCT Applicant's Guide.

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer
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Facsimile No. (41-22) 740.14.35

J. Zahra

Telephone No. (41-22) 338.83.38

PATENT COOPERATION TREATY

PCT

NOTIFICATION OF ELECTION
(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

United States Patent and Trademark
Office
(Box PCT)
Crystal Plaza 2
Washington, DC 20231
ÉTATS-UNIS D'AMÉRIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 14 June 1999 (14.06.99)

International application No. PCT/CA97/00745	Applicant's or agent's file reference 2139-11 PCT
International filing date (day/month/year) 15 October 1997 (15.10.97)	Priority date (day/month/year)

Applicant KONISHI, Yasuo et al

1. The designated Office is hereby notified of its election made:

in the demand filed with the International Preliminary Examining Authority on:

13 May 1999 (13.05.99)

in a notice effecting later election filed with the International Bureau on:

2. The election was

was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer S. Mafla Telephone No.: (41-22) 338.83.38
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PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 14/815, A61K 38/58	A1	(11) International Publication Number: WO 99/19356 (43) International Publication Date: 22 April 1999 (22.04.99)
(21) International Application Number: PCT/CA97/00745 (22) International Filing Date: 15 October 1997 (15.10.97) (71) Applicant (<i>for all designated States except US</i>): NATIONAL RESEARCH COUNCIL OF CANADA [CA/CA]; Building M-58, Rm EG-12, 1200 Montreal Road, Ottawa, Ontario K1A 0R6 (CA). (72) Inventors; and (75) Inventors/Applicants (<i>for US only</i>): KONISHI, Yasuo [CA/CA]; 17130 Brunswick Boulevard, Kirkland, Quebec H9J 1K8 (CA). SLON, Jacek [CA/CA]; 8405 Bougainville Avenue #301, Montreal, Quebec H4P 2G6 (CA). (74) Agent: COTE, France; Swabey Ogilvy Renault, Suite 1600, 1981 McGill College Avenue, Montreal, Quebec H3A 2Y3 (CA).	(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>	
(54) Title: TRIVALENT THROMBIN INHIBITOR		
(57) Abstract		
<p>The present invention relates to a new thrombin inhibitor of formula (I) comprising an S subsite blocking segment (AS), an S' subsite blocking segment (Z), and a fibrinogen recognition exosite blocking segment (P). AS is linked to Z, which is linked to P according to the formula (1): AS-Z-P. The S' subsite blocking segment thus, besides binding to the thrombin S' subsites, connects the S subsite blocking segment and the fibrinogen recognition exosite blocking segment. This binding of Z segment together with the bindings of the AS and P segments, contributes to improve the affinity of the inhibitors significantly.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AL	Albania	ES	Spain	LS	Lesotho	SI	Slovenia
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DE	Germany	LK	Sri Lanka	SE	Sweden		
DK	Denmark	LR	Liberia	SG	Singapore		

INTERNATIONAL SEARCH REPORT

Internal Application No
PCT/CA 97/00745

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K14/815 A61K38/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	<p>SZEWCZUK E.A.: "Design of a linker for trivalent thrombin inhibitors; interaction of the main chain of the linker with thrombin" BIOCHEMISTRY, vol. 32, no. 13, 6 April 1993, EASTON, PA US, pages 3396-3404, XP002067819 see the whole document</p> <p>---</p> <p style="text-align: center;">-/-</p>	1-4,7-14

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

Date of mailing of the international search report

12 June 1998

15.07.1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Groenendijk, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 97/00745

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TSUDA E.A.: "Design of potent bivalent thrombin inhibitors based on hirudin sequence: incorporation of nonsubstrate-type active site inhibitors" BIOCHEMISTRY, vol. 33, no. 48, 6 December 1994, EASTON, PA US, pages 14443-14451, XP002067820 see the whole document ---	1-4,7-14
Y	WO 95 11921 A (NAT RESEARCH COUNCIL CANADA NR ;KONISHI YASUO (CA); SZEWCZUK ZBIGN) 4 May 1995 see the whole document ---	1-4,7-14
A	KRISHNAN: "Synthesis, structure and structure-activity relationships of divalent thrombin inhibitors containing an alpha-keto-amide transition-state mimic" PROTEIN SCIENCE, vol. 5, no. 3, March 1996, pages 422-433, XP002067821 -----	1-14

INTERNATIONAL SEARCH REPORT

International application No.
PCT/CA 97/00745

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internal Application No

PCT/CA 97/00745

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 9511921 A	04-05-1995	AU 7935494 A	CA 2175388 A	EP 0725797 A

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 2139-11 PCT	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/CA 97/ 00745	International filing date (day/month/year) 15/10/1997	(Earliest) Priority Date (day/month/year)
Applicant NATIONAL RESEARCH COUNCIL OF CANADA et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 4 sheets.

It is also accompanied by a copy of each prior art document cited in this report.

1. Certain claims were found unsearchable (see Box I).
2. Unity of invention is lacking (see Box II).
3. The international application contains disclosure of a nucleotide and/or amino acid sequence listing and the international search was carried out on the basis of the sequence listing
 - filed with the international application.
 - furnished by the applicant separately from the international application,
 - but not accompanied by a statement to the effect that it did not include matter going beyond the disclosure in the international application as filed.
 - Transcribed by this Authority
4. With regard to the title,
 - the text is approved as submitted by the applicant.
 - the text has been established by this Authority to read as follows:
5. With regard to the abstract,
 - the text is approved as submitted by the applicant.
 - the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this International Search Report, submit comments to this Authority.
6. The figure of the drawings to be published with the abstract is:

Figure No. _____	<input type="checkbox"/> as suggested by the applicant.	<input checked="" type="checkbox"/> None of the figures.
	<input type="checkbox"/> because the applicant failed to suggest a figure.	
	<input type="checkbox"/> because this figure better characterizes the invention.	

INTERNATIONAL SEARCH REPORT

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 13 and 14 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/CA 97/00745

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K14/815 A61K38/58

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X, Y	<p>SZEWCZUK E.A.: "Design of a linker for trivalent thrombin inhibitors; interaction of the main chain of the linker with thrombin" BIOCHEMISTRY, vol. 32, no. 13, 6 April 1993, EASTON, PA US, pages 3396-3404, XP002067819 see the whole document</p> <p>---</p> <p>-/-</p>	1-4,7-14

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

° Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

12 June 1998

Date of mailing of the international search report

15.07.1998

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
 NL - 2280 HV Rijswijk
 Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
 Fax: (+31-70) 340-3016

Authorized officer

Groenendijk, M

INTERNATIONAL SEARCH REPORT

International Application No

PCT/CA 97/00745

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	TSUDA E.A.: "Design of potent bivalent thrombin inhibitors based on hirudin sequence: incorporation of nonsubstrate-type active site inhibitors" BIOCHEMISTRY, vol. 33, no. 48, 6 December 1994, EASTON, PA US, pages 14443-14451, XP002067820 see the whole document ---	1-4,7-14
Y	WO 95 11921 A (NAT RESEARCH COUNCIL CANADA NR ;KONISHI YASUO (CA); SZEWCZUK ZBIGN) 4 May 1995 see the whole document ---	1-4,7-14
A	KRISHNAN: "Synthesis, structure and structure-activity relationships of divalent thrombin inhibitors containing an alpha-keto-amide transition-state mimic" PROTEIN SCIENCE, vol. 5, no. 3, March 1996, pages 422-433, XP002067821 -----	1-14

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/CA 97/00745

Patent document cited in search report	Publication date	Patent family member(s)		Publication date			
WO 9511921 A	04-05-1995	AU 7935494 A	22-05-1995	CA 2175388 A	04-05-1995	EP 0725797 A	14-08-1996

PATENT COOPERATION TREATY

PCT

REC'D 21 JAN 2000

WIPO PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2139-11 PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA97/00745	International filing date (day/month/year) 15/10/1997	Priority date (day/month/year) 15/10/1997
International Patent Classification (IPC) or national classification and IPC C07K14/815		
Applicant NATIONAL RESEARCH COUNCIL OF CANADA et al.		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.		
2. This REPORT consists of a total of 5 sheets, including this cover sheet.		
<input type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).		
These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items:		
<ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input checked="" type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 		

Date of submission of the demand 13/05/1999	Date of completion of this report 17. 01. 00
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Zellner, E Telephone No. +49 89 2399 8427



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA97/00745

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-30 as originally filed

Claims, No.:

1-14 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-14
Industrial applicability (IA)	Yes:	Claims	1-12
	No:	Claims	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA97/00745

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA97/00745

Item V

1. Reference is made to the following documents:

D1: Biochemistry, 1993, 32, 3396-3404
D2: Biochemistry, 1994, 33, 14443-14451
D3: WO-A-9 511 921

2. The present application refers to trivalent thrombin inhibitors of the structure AS-Z-P as defined in Claim 1. The distinguishing feature of the thrombin inhibitor of the present claims and those of the prior art is Z representing a S' subsite blocking segment which links AS and P.

In D1 the linker consists of about 4 to 6 amino acids as represented in Table I (page 3399) such as GlnSerHisAsnAspGly, GlyGlyGlyGlyGly or GlyGlyGlyGlyGly whereas in the present claims the linker consists of 5 amino acids for example GlyGlyAlaGly β Ala. The features distinguishing the linkers of the present application and those of D1 is that β -Ala is at the end of the linker and that only non-polar amino acids are at position 1 and 3 of the linker in the present application. In D1 a polar amino acid such as Gln can be at position 1.

In the general part of the application it is asserted that said non-polar amino acids in the S' subsite blocking segment lead to an improved affinity of the thrombin inhibitor.

However, it is not demonstrated whether at least a broad range of the linkers of present application have indeed a higher affinity than the linkers of D1.

Therefore an objection under lack of inventive step (Article 33 (3) PCT) has to be raised.

If it is demonstrated in the regional phase that all linkers of the present application are indeed advantageous in comparison with the linkers of D1, inventive step can be acknowledged.

D2 and D3 do not appear to be relevant under Article 33 (2) and (3) EPC, since the linkers are more complex and not similar to those of the present application.

3. Claims 13 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA97/00745

claims (Article 34(4)(a)(i) PCT).

Item VII

In the description (page 10, lines 20-23) it is stated that β -Ala can be substituted with other amino acids. Therefore the linker of Claim 1 include linkers not distinguished from those of D1 such as the P198 GlyGlyGlyGlyGly linker in Table I. Therefore said passage of the description should be deleted. The same applies to page 18, lines 5-10).

REC'D URGENT
JAN 24 2000

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

COTE, France
SWABEY OGILVY RENAULT
1981 McGill College Avenue
Suite 1600
Montréal, Québec H3A 2Y3
CANADA

A.M. | 8 | 9 | 10 | 11 | 12 | 1 | 2 | 3 | 4 | 5 |
P.M.
PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing
(day/month/year)

17.01.00

Applicant's or agent's file reference
2139-11 PCT

IMPORTANT NOTIFICATION

International application No. PCT/CA97/00745	International filing date (day/month/year) 15/10/1997	Priority date (day/month/year) 15/10/1997
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Applicant
NATIONAL RESEARCH COUNCIL OF CANADA et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Vullo, C Tel. +49 89 2399-8061	
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PATENT COOPERATION TREATY
PCT
INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 2139-11 PCT	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/CA97/00745	International filing date (day/month/year) 15/10/1997	Priority date (day/month/year) 15/10/1997	
International Patent Classification (IPC) or national classification and IPC C07K14/815			
Applicant NATIONAL RESEARCH COUNCIL OF CANADA et al.			

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.

This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I Basis of the report
- II Priority
- III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV Lack of unity of invention
- V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI Certain documents cited
- VII Certain defects in the international application
- VIII Certain observations on the international application

Date of submission of the demand 13/05/1999	Date of completion of this report 17.01.00
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Zellner, E Telephone No. +49 89 2399 8427



**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA97/00745

I. Basis of the report

1. This report has been drawn on the basis of (*substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments.*):

Description, pages:

1-30 as originally filed

Claims, No.:

1-14 as originally filed

2. The amendments have resulted in the cancellation of:

the description, pages:
 the claims, Nos.:
 the drawings, sheets:

3. This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

4. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims 1-14
	No: Claims
Inventive step (IS)	Yes: Claims
	No: Claims 1-14
Industrial applicability (IA)	Yes: Claims 1-12
	No: Claims

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. PCT/CA97/00745

2. Citations and explanations

see separate sheet

VII. Certain defects in the international application

The following defects in the form or contents of the international application have been noted:

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA97/00745

Item V

1. Reference is made to the following documents:

D1: Biochemistry, 1993, 32, 3396-3404
D2: Biochemistry, 1994, 33, 14443-14451
D3: WO-A-9 511 921

2. The present application refers to trivalent thrombin inhibitors of the structure AS-Z-P as defined in Claim 1. The distinguishing feature of the thrombin inhibitor of the present claims and those of the prior art is Z representing a S' subsite blocking segment which links AS and P.

In D1 the linker consists of about 4 to 6 amino acids as represented in Table I (page 3399) such as GlnSerHisAsnAspGly, GlyGlyGlyGlyGly or GlyGlyGlyGlyGly whereas in the present claims the linker consists of 5 amino acids for example GlyGlyAlaGly β Ala. The features distinguishing the linkers of the present application and those of D1 is that β -Ala is at the end of the linker and that only non-polar amino acids are at position 1 and 3 of the linker in the present application. In D1 a polar amino acid such as Gln can be at position 1.

In the general part of the application it is asserted that said non-polar amino acids in the S' subsite blocking segment lead to an improved affinity of the thrombin inhibitor.

However, it is not demonstrated whether at least a broad range of the linkers of present application have indeed a higher affinity than the linkers of D1.

Therefore an objection under lack of inventive step (Article 33 (3) PCT) has to be raised.

If it is demonstrated in the regional phase that all linkers of the present application are indeed advantageous in comparison with the linkers of D1, inventive step can be acknowledged.

D2 and D3 do not appear to be relevant under Article 33 (2) and (3) EPC, since the linkers are more complex and not similar to those of the present application.

3. Claims 13 and 14 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/CA97/00745

claims (Article 34(4)(a)(i) PCT).

Item VII

In the description (page 10, lines 20-23) it is stated that β -Ala can be substituted with other amino acids. Therefore the linker of Claim 1 include linkers not distinguished from those of D1 such as the P198 GlyGlyGlyGlyGly linker in Table I.

Therefore said passage of the description should be deleted. The same applies to page 18, lines 5-10).